Background and Objectives of Ongoing Studies

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Perchlorate Stakeholders Forum
Sponsored by the IPSC
Henderson, NV
19-21 May 1998

I P S C

Outline

- Background
  - Definition of the RfD
  - Derivation of the RfD
  - Basis of the provisional RfD
- Review of perchlorate database
- Recommended new studies
  - Description of different study designs
  - Objectives of each study
  - Strategy for synthesis of data
- Summary

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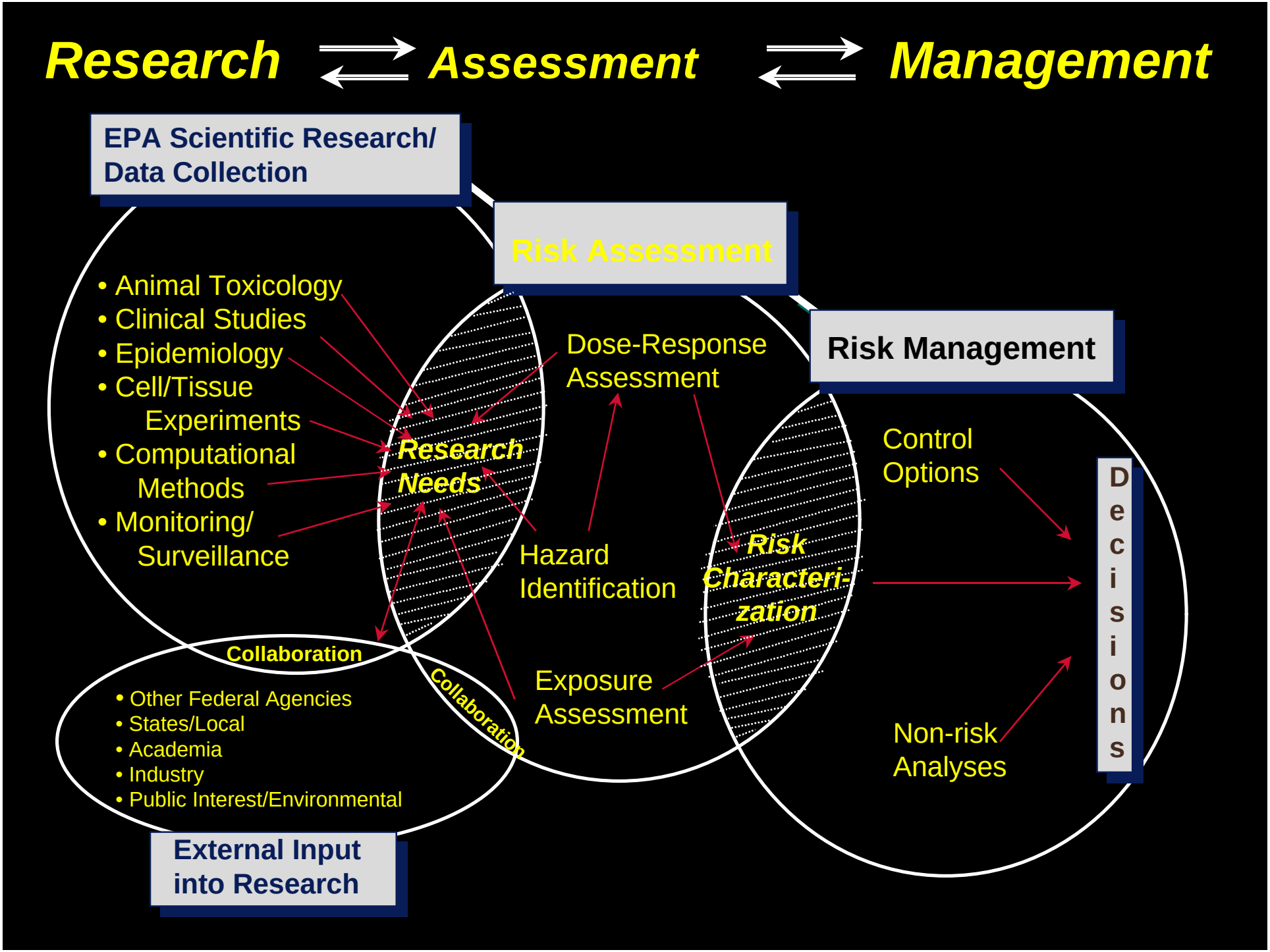
Definition

An oral reference dose (RfD) is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer health effects during a lifetime.


Research
Assessment
Management
EPA Scientific Research/
Data Collection
Risk Assessment
Risk Management
• Animal Toxicology
• Clinical Studies
• Epidemiology
• Cell/Tissue
Experiments
• Computational
Methods
• Monitoring/
Surveillance
Research
Needs
Dose-Response
Assessment
Hazard
Identification
Risk
Characteri-
zation
Control
Options
Decisions
Exposure
Assessment
Non-risk
Analyses
Collaboration
Collaboration
• Other Federal Agencies
• States/Local
• Academia
• Industry
• Public Interest/Environmental
External Input
into Research

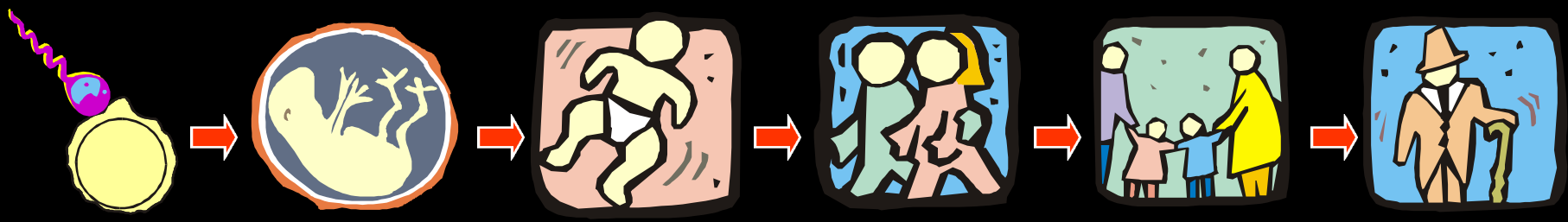
Minimum Data Base for Derivation of an RfD

Mammalian Data Base**	Confidence	Comments
A. Two Chronic Oral Bioassays in Different Species B. One 2-Generation Reproductive Study C. Two Developmental Toxicity Studies in Different Species	High*	Minimum Data Base for High Confidence
One Subchronic Oral Bioassay	Low	Minimum Data Base for Estimation of an RfD

* Rationale is to address all potentially critical life stages

** Rationale is to use different species to evaluate variability in species sensitivity unless a particular laboratory animal model is more appropriate

A High Confidence RfD is Based on Data that Addresses All Potentially Critical Life Stages.



Reproductive

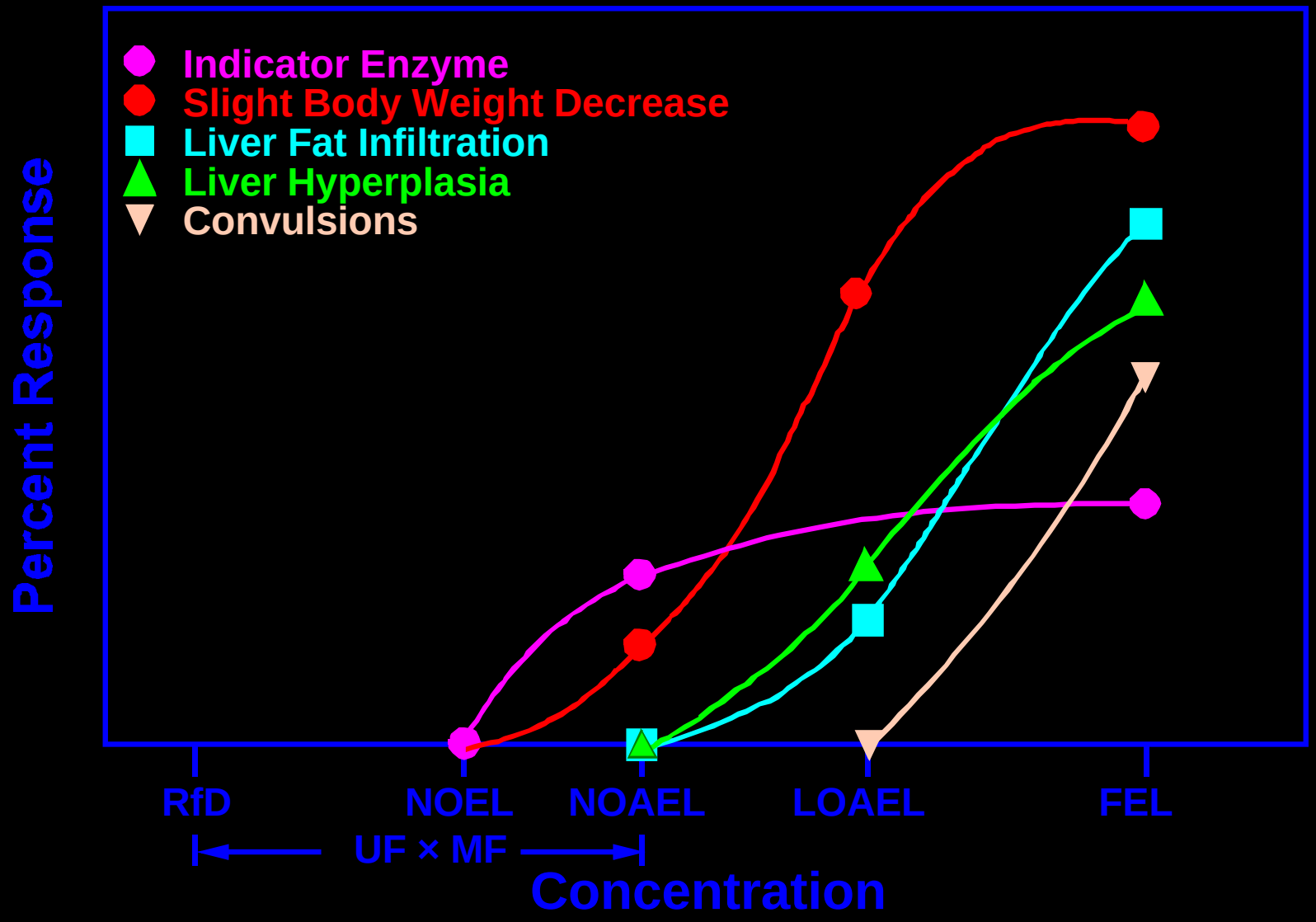
Developmental

General Toxicity

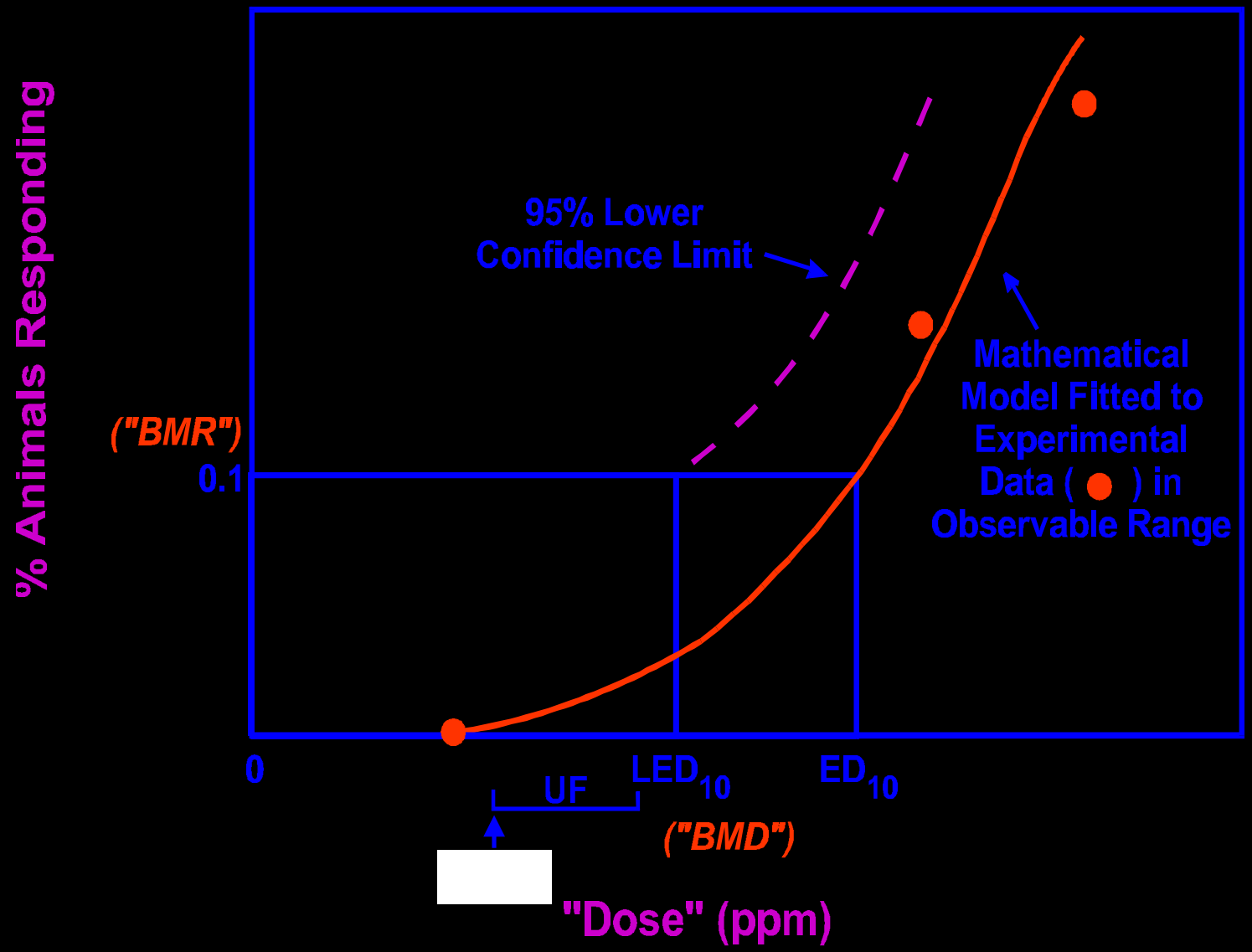
RfD Derivation

- Hazard identification and data array analysis
- Designation of effect levels (NOAEL, BMD)
- Choice of critical effect
- Dosimetric adjustment
- Application of uncertainty factors (UF)
- Characterization of uncertainty (confidence levels)

Data Array and Oral Reference Dose (RfD) Derivation



"Benchmark Dose" Approach to Dose-Response Analysis for Noncancer Endpoints



$$RfC = \frac{NOAEL^{*}[HED]}{UF \times MF}$$

Where:

NOAEL*[HED] =

The NOAEL or equivalent effect level obtained with an alternate approach (*), dosimetrically-adjusted to a human equivalent dose [HED].

UF =

Uncertainty factor(s) applied to account for the extrapolation required from the characteristics of the experimental regimen to the assumed human scenario, and

MF =

Modifying factor to account for scientific uncertainties in the study(ies) chosen as the basis for the operational derivation, e.g., poor statistical power or exposure characterization.

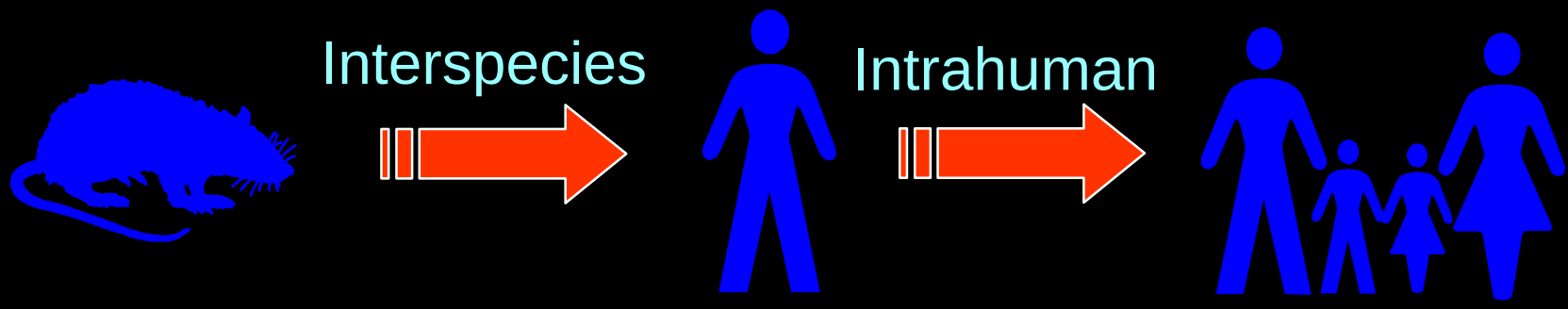
Factors for Uncertainties in Applied Extrapolations

10_H	Human to Sensitive Human
10_A	Experimental Animal to Human
10_S	Subchronic to Chronic Duration
10_L	LOAEL(HEC) to NOAEL(HEC)
10_D	Incomplete to Complete Data Base

Modifying Factor

MF Professional Assessment of Scientific Uncertainties of the Study and Data Base not Explicitly Addressed Above. Default for the MF is 1.0 e.g., applied for small sample size or poor exposure characterization.

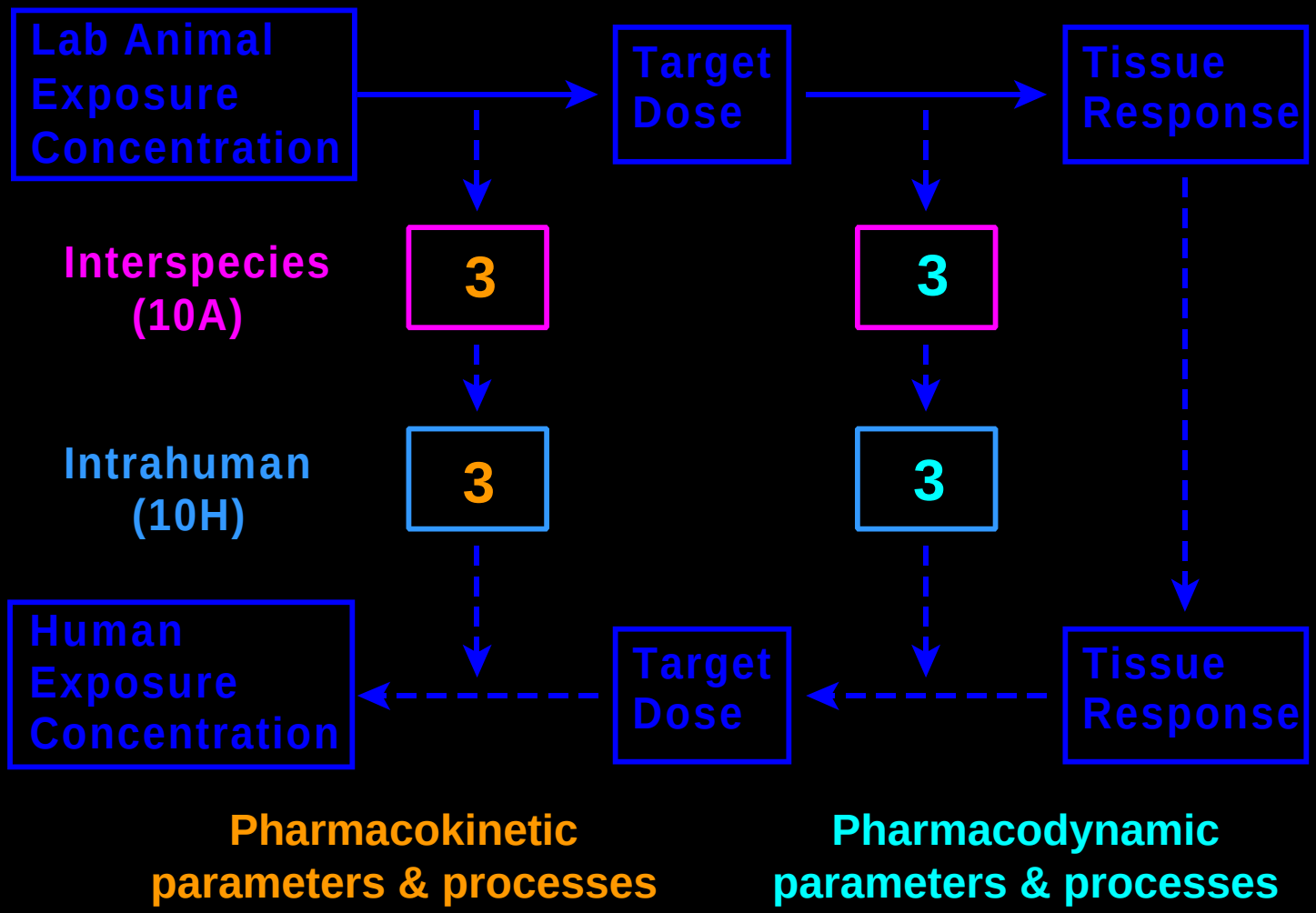
Extrapolation Uncertainties



Rat to Human

Variability Across Humans

Schematic of UF Components Incorporated Into Exposure-Dose-Response Characterization



Basis of the Provisional RfD

- **Initial correspondence to EPA Region IX (Dec 92) from Superfund Health Risk Technical Support Center (NCEA-Cin)**
- **Principal study = Stanbury & Wyngaarden (1952)**
- **NOAEL = 0.14 mg/kg-day for 100% iodide release**
- **UF = 1000**
  - intrahuman variability (10)
  - less than chronic data (10)
  - database deficiencies (10)
- **Drinking water criteria = 3.5 ppb based on 70 kg / 2 L water**

Second Provisional RfD (1995)

- **Revision based on PSG submission to Superfund Health Risk Technical Support Center (NCEA-Cin)**
- **Same principal study and NOAEL**
- **Different UF**
  - intrahuman variability (10)
  - less than chronic data (10)
  - database deficiencies decreased (3)
- **Drinking water criteria = 18 ppb based on 70 kg / 2 L water**

Provisional RfD
March 1997
External Peer Review

- **Proposed by TERA**
- **Same prinicipal study, critical effect**
- **Another, different UF = 100**
  - intrahuman reduced (3)
  - subchronic to chronic (3)
  - LOAEL to NOAEL (3)
  - Database deficiencies (3)

March 1997
External Peer Review Process

- Independent experts selected from government, industry, academia, consulting firms and environmental groups by TERA Board of Trustees
- Conflict of interest disclosed and discussed
- Review lasted 3 hours and included:
  - presentation by sponsor
  - discussion by review panel of database, hazard identification, dose-response derivation, and other issues
  - opportunity for registered observers to comment
  - polling panel for consensus
  - identification of outstanding issues

March 1997 External Peer Reviewers

- Dr. Robert Benson, U.S. EPA, Region VIII
- Dr. John Christopher*, California EPA
- Dr. Gary Diamond, Syracuse Research Corporation
- Dr. Marvin Friedman, Cytec Industries, Inc.
- Ms. Annie Jarabek, U.S. EPA, National Center for Environmental Assessment
- Ms. Bette Meek, Health Canada
- Dr. Kenneth Poirier, Procter and Gamble Company
- Dr. Jon Reid, University of Cincinnati
- Ms. Ruthann Rudel, Silent Spring Institute
- Experts Available to Peer Review Panel
  - Dr.James Fagin, University of Cincinnati Department of Endocrinology
  - Dr. Charles Capen, Ohio State University Department of Veterinary Biosciences
  - Dr. Daniel Caldwell, principal investigator of the Caldwell et al. (1996) study

* Dr. Christopher was not polled for consensus

March 1997
External Peer Review

- Inadequate data base for derivation
- Available mechanistic insights suggest special studies and synthesis strategy
- Eight (8) additional new categories of studies recommended

Deficiencies of Clinical Data

- Adult subjects
- Typically subjects with thyroids altered by disease or other treatments
- Few pregnant subjects
- Acute or short-term exposure duration
- Limited range of doses

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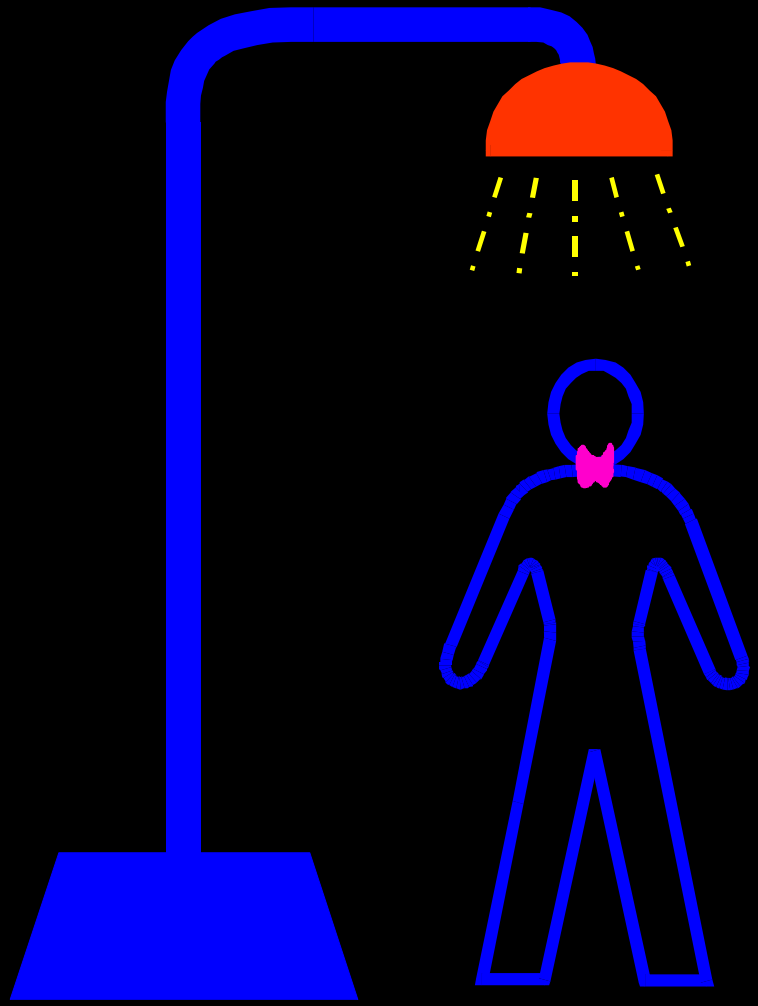
Established Perchlorate Toxicity



The only systematically studied and established effect is the anti-thyroid effect due to competitive inhibition of iodine uptake.

Susceptibility

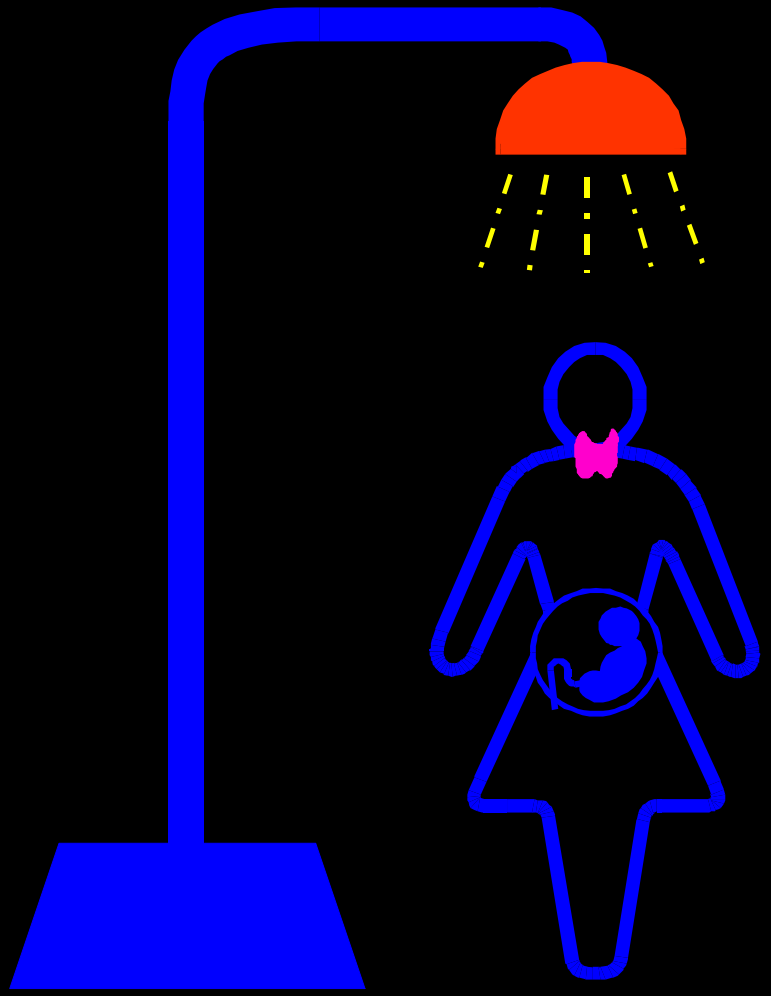
The potential for increased susceptibility is due to factors that influence:

(1) **Exposure e.g., activity patterns and location**

(2) **Deposition / uptake and the internal target tissue dose (i.e., pharmacokinetic parameters) and toxicant-target interactions, e.g., metabolism rates or pathways**

(3) **Tissue sensitivity (pharmacodynamics) - conditions which alter or enhance target tissue response, e.g., age, nutritional status, or disease states**

Potential Perchlorate Toxicity



Anti-thyroid effect in pregnant women might cause adverse effect in developing fetus.

Additional Suggested Target Tissues

- Reproductive function
- Immune function
  - aplastic anemia
  - leukopenia

Mechanisms of Anti-Thyroid Mediated Neoplasia in Rodents

- DNA Directed:
  - X - rays
  - 131 I
  - Genotoxic chemicals
- Indirect
  - Partial thyroidectomy
  - Transplantation of TSH-secreting pituitary tumors
  - Iodide deficiency
  - Chemicals inhibiting iodide uptake
  - Chemicals inhibiting thyroid peroxidase
  - Chemicals inhibiting TH
  - Chemicals inhibiting conversion of T3 & T4
  - Chemical inhibiting hepatic thyroid hormone metabolism and excretion

Mode of Action Provides Important Insight to Characterization of Toxicity

- A chemical's influence on the molecular, cellular, and physiological functions in producing tumors
- Prolonged depression of TH causes a feedback that leads to upregulation of TSH which leads to thyroid gland hyperplasia
- Genotoxic?

Proliferative Lesions Thyroid Follicular Cells in Rodents

Normal

Hyperplasia

Adenoma

Carcinoma

Significance in Risk Assessment

Existing Data Summary

- Target tissue appears to be the thyroid but available testing not comprehensive across endpoints
- Anti-thyroid effects would differ among adult versus developing fetus, children
- Anti-thyroid effects associated with benign neoplasia development in rats; a nonlinear process
- Genotoxicity not characterized
- Relevancy to human risk of rat tumors not established; presumed protective

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Recommended Studies

- 90-Day subchronic bioassay
- Developmental neurotoxicity study
- Genotoxicity assays
- Mechanistic studies
- ADME - Absorption, Distribution, Metabolism and Elimination
- Developmental study
- 2-Generation reproductive toxicity study
- Immunotoxicity

90-Day Subchronic Bioassay

- Tests for additional target tissues
- Minimum database for RfD derivation
- Added additional tests for:
  - reproductive parameters
  - mutagenic effects in bone marrow
  - thyroid hormone levels
  - recovery
- Objective is to ascertain if anti-thyroid effect is critical and its dose-response

Developmental Neurotoxicity Study in Rats

- Examines potentially critical effect and population: evaluates nervous system (structure and function) of fetal, newborn, and young animals
- Added thyroid histopathology and thyroid hormone level determinations to characterize anti-thyroid effect in offspring

Genotoxicity Assays

- Tests for toxicity to DNA
- Provides mode-of-action information to evaluate potential for carcinogenicity
- May impact consideration of uncertainty factor for less than chronic data

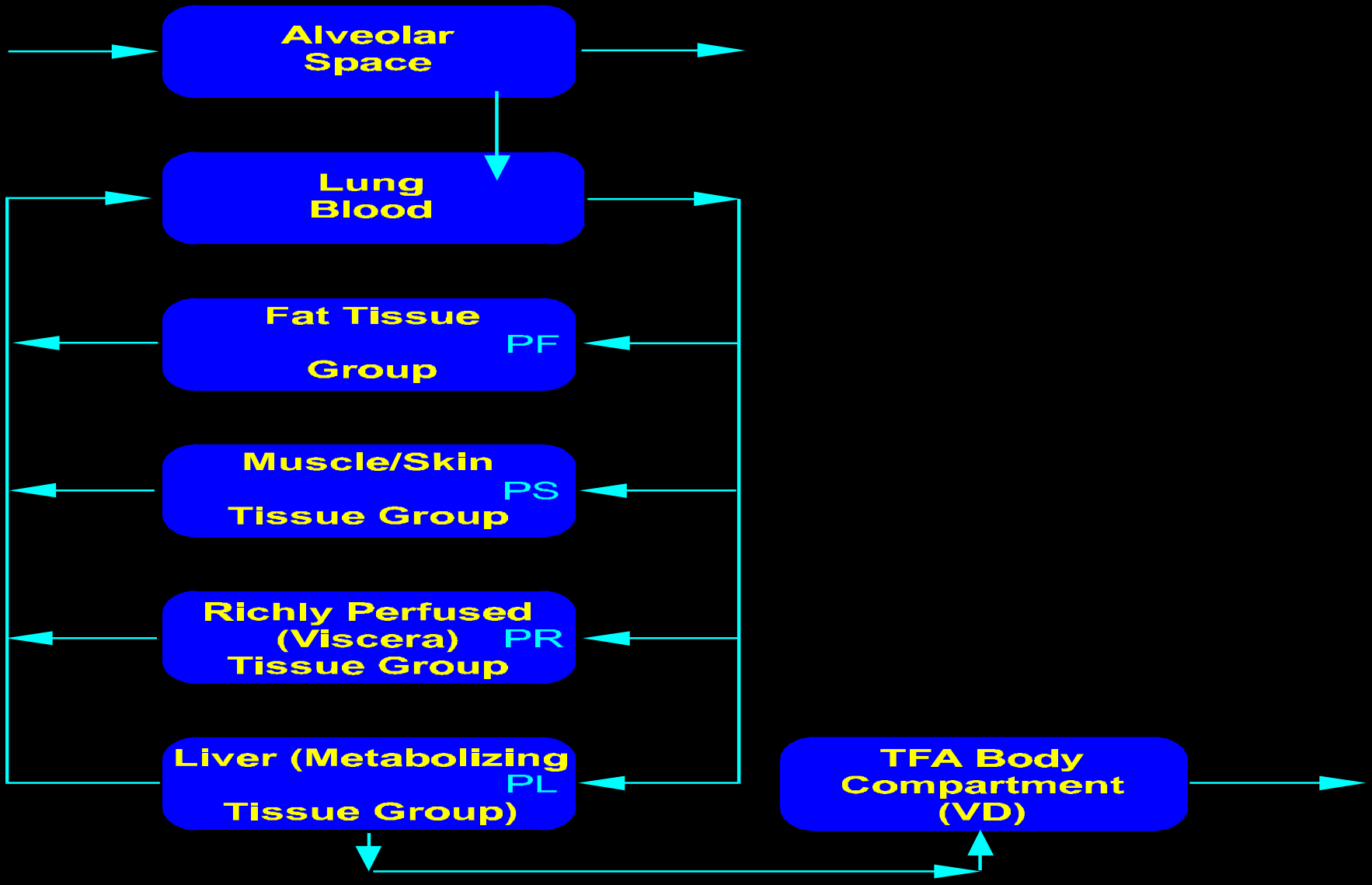
Mechanistic Studies

- Aid to quantitative interspecies extrapolation - basis to extend PBPK model
- Additional developmental studies to evaluate thyroid TH in fetal and post-natal periods
- Determine relative sensitivity of fetal/postnatal thyroid versus adult
- Determine relative sensitivity of rat versus human

ADME study

- Literature review of perchlorate discharge test
- Protocols proposed to evaluate perchlorate kinetics, iodine inhibition kinetics and thyroid hormone homeostasis
- Basis for development of physiologically-based pharmacokinetic (PBPK) model

PBPK Model Schematic



Developmental Study in Rabbits

- Endpoint required for greater confidence in database, may reduce UF for data deficiencies if not critical effect
- Definitive test for toxicity during organ development (birth defects)
- Added additional groups, hormone analysis and thyroid histopathology to evaluate second species

2-Generation Reproductive Toxicity Study

- Evaluates fertility of adults and viability of (toxicity in) offspring in rats
- Tests for reproductive parameters over two generations
- Added analysis of thyroid hormones and thyroid histopathology at various time points
- Endpoint required for greater confidence in database, may reduce UF for database deficiencies if not critical effect

Immunotoxicity Study

- Evaluates immune system structure and function
- Motivated by case reports of aplastic anemia and leukopenia
- May reduce UF for database deficiencies if not critical effect

Recommended Studies Summary

Study	Description	Use in assessment
1. Developmental neurotoxicity + TH	Evaluates nervous system in fetal and postnatal rats	Potentially critical effect; comparison of developmental versus adult effects on TH
2. 90-Day subchronic bioassay + TH + repro + genotox + recovery	Tests for other target tissues; evaluates effect on TH in young adult rats	Minimum database for RfD dose-response for TH in young adult rats; additional info on other; may allow decrease in UF for database deficiencies
3. Genotoxicity assays	Tests for toxicity to DNA	Mode of action information for thyroid neoplasia; may reduce UF for database deficiencies
4. Mechanistic studies	Evaluate mechanism of TH response and sensitivity in rats and humans	Interspecies extrapolation; determine susceptible subpopulation

Recommended Studies Summary

Study	Description	Use in assessment
5. ADME studies	Characterizes absorption, distribution, metabolism and elimination in rats and humans; iodine inhibition and perchlorate kinetices, hormone homeostasis	Interspecies extrapolation
6. Developmental study + TH	Evaluates birth defects in rabbits	Potentially critical effect; data in second species for TH effects; may reduce UF for database deficiencies
7. 2 - Generation reproductive toxicity + TH	Evaluates fertility of adult rats and toxicity in offspring over two generations	Potentially critical effect; may reduce UF for database deficiencies
8. Immunotoxicity	Evaluates immune system structure and function	May reduced UF for database deficiencies if not critical effect

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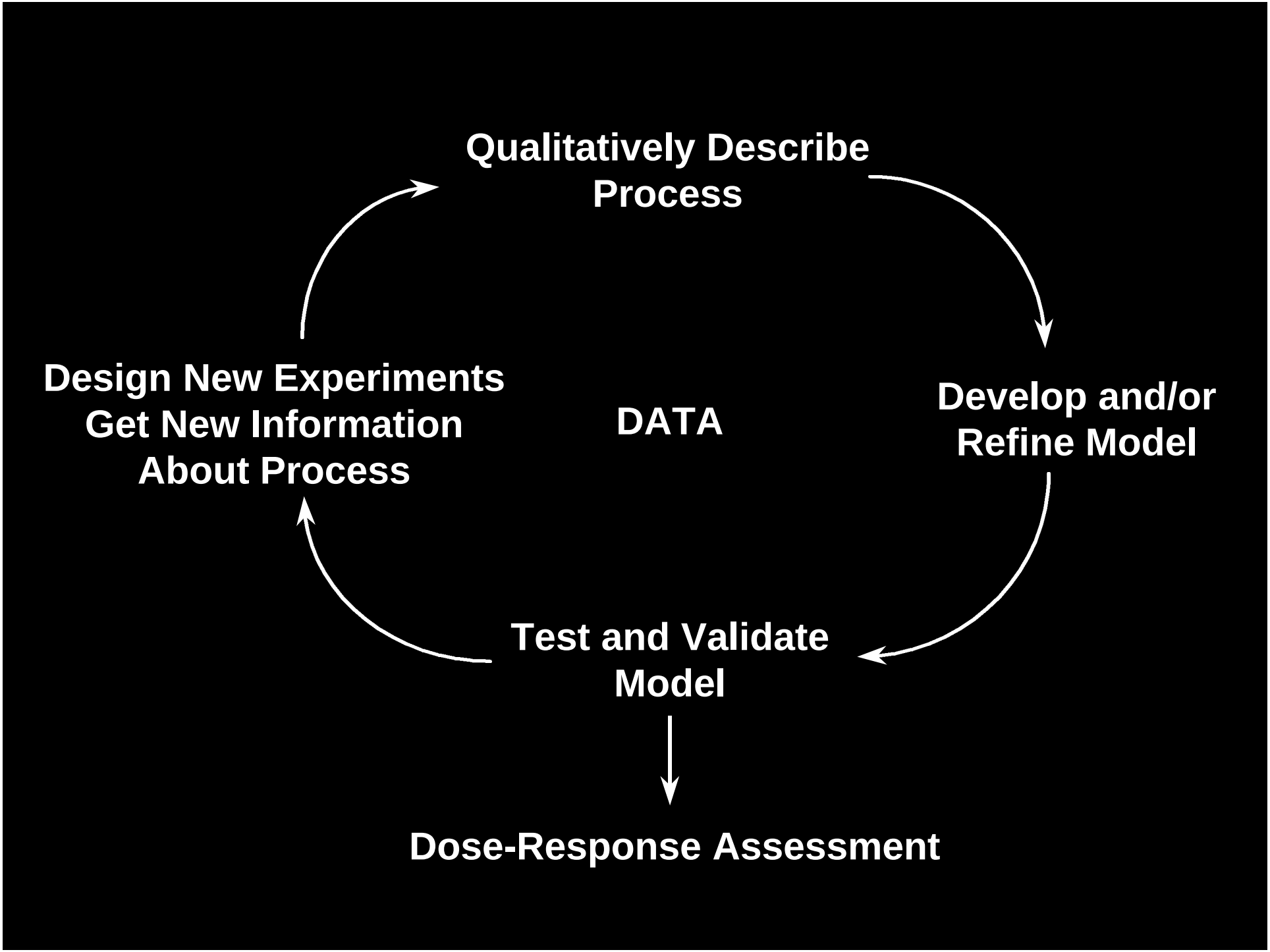
Revised RfD

- Data across comprehensive array of endpoints to establish target tissue
- Mechanistically-motivated special studies to characterize critical dose-response relationships
- Future refinements as required by new data


Qualitatively Describe Process
Develop and/or Refine Model
Test and Validate Model
Dose-Response Assessment
Design New Experiments Get New Information About Process
DATA

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